JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

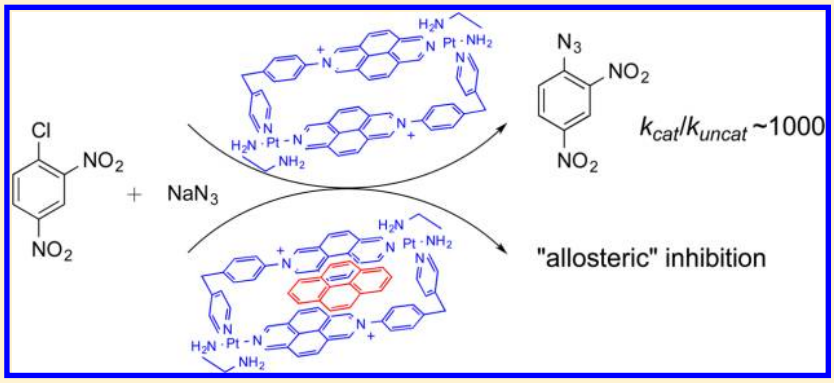
Metallacycle-Catalyzed S_NAr Reaction in Water: Supramolecular Inhibition by Means of Host–Guest Complexation

Eva M. López-Vidal,[†] Antonio Fernández-Mato,[†] Marcos D. García,[†] Moisés Pérez-Lorenzo,[‡] Carlos Peinador,*[,†] and José M. Quintela*[,†]

[†]Departamento de Química Fundamental and Centro de Investigaciones Científicas Avanzadas (CICA), Facultad de Ciencias, Universidade da Coruña, A Zapateira s/n, 15008 A Coruña, Spain

[‡]Departamento de Química Física, Universidade de Vigo, 36310 Vigo, Spain

Supporting Information



ABSTRACT: The performance of a Pt^{II} diazapyrenium-based metallacycle as a reusable substoichiometric catalyst for the S_NAr reaction between halodinitrobenzenes and sodium azide at rt in aqueous media is reported. The results suggest that the catalytic effect is promoted by the association of the azide to the diazapyrenium cationic subunits of the catalyst. The findings demonstrate that the formation of an inclusion complex between pyrene and the metallacycle has a regulatory effect over the system, resulting in allosteric-like inhibition of the S_NAr reaction.

INTRODUCTION

The high diversity of regulation mechanisms found in enzymatic reactions has become a major source of inspiration for the design of abiotic systems with efficient and controlled catalytic activity.[1] In this regard, coordination-driven self-assembly has enabled the rational preparation of a myriad of 2D/3D metallacycles with diverse potential purposes,[2] including the development of a substantial amount of cavity-controlled reactions.[3] In most cases, the peculiar chemical environment created within the inner cavities of these hosts is exploited to create supramolecular catalytic systems that use encapsulation of reactants to decrease the entropic penalty of a given reaction. However, the use of metallacycles as efficient catalysts has rarely been demonstrated, as in many cases they bind products as effectively as reactants, thereby inhibiting the catalytic turnover.[4] Moreover, few examples where the catalytic activity can be controlled by means of regulatory effectors have been reported.[5]

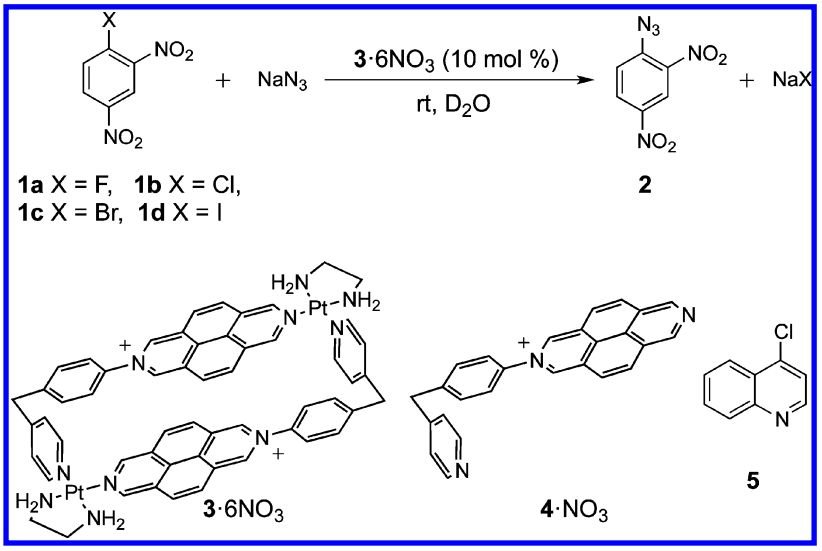
Over the past few years, by using *N*-monoalkyl-2,7-diazapyrenium salts and square-planar Pt^{II} metals, our research group has developed a coordination-driven self-assembly approach for the preparation of 2D metallacycles.[6] In order to explore the potential of our designed molecular hosts in the field of catalysis, we decided to study the effect of the Pt^{II} diazapyrenium-based metallacycle **3** on a nucleophilic aromatic substitution (S_NAr) (Scheme 1). A priori, as a result of the special characteristics of the diazapyrenium-containing metallacycle **3**, it can act as catalyst for the S_NAr through cation-induced desolvation of the anionic nucleophile.[7] Moreover, its central cavity would be suitable to accommodate aromatic substrates,[8] a fact that could potentially alter their reactivity in the S_NAr.[4c] Finally, we anticipated that the cavity of the metallacycle could also act as a regulation center for the catalytic system, as appropriate aromatic nonreactive compounds could be complexed by **3**, altering in that manner the catalysis.

In the work presented herein, we demonstrate that metallacycle **3** efficiently catalyzes the S_NAr reaction between halodinitrobenzenes and sodium azide in aqueous media by means of nucleophile desolvation, which was found to be caused by the diazapyrenium ligands within the metallacycle structure. Furthermore, inclusion of a suitable guest for **3** in the system results in deactivation of the catalysis as a result of host–guest interactions.

Received: December 4, 2013
Published: January 20, 2014

dx.doi.org/10.1021/jo402689p | J. Org. Chem. 2014, 79, 1265–1270

Scheme 1. Model S_NAr Reaction and Species Discussed in This Work



RESULTS AND DISCUSSION

As model for the S_NAr, we examined the reaction between halodinitrobenzenes **1a–d** and sodium azide (10 equiv) in D_2O at rt in the presence or absence of catalytic amounts of the water-soluble metallacycle **3**·6NO_3 (Scheme 1). Control reactions in the absence of **3**·6NO_3 showed that **1a** was transformed into the expected azide **2** (100% conversion in 22 h, as determined by ^1H NMR analysis of a $CDCl_3$ extract). On the contrary, no reaction product at all was detected after 24 h in the $CDCl_3$ extracts for **1b–d**. These reactions proceeded rather slowly, with low conversions achieved only after 8 days (X = Cl, 33%; X = Br, 44%; X = I, 23%). Remarkably, the use of **3**·6NO_3 as catalyst dramatically changed the reactivity of **1b–d** in water: after 20 h, no starting material was detected, and azide **2** was the only reaction product.

Kinetic studies of the reaction between **1b** (6 mM) and sodium azide (60 mM) were carried out at rt in D_2O/CD_3CN (4:1).[9] As expected, the reaction for **1b** was much faster in presence of **3**·6NO_3 (0.6 mM, 10 mol %) compared with the control reaction (Figure 1). Unsurprisingly, ligand **4**·NO_3 (1.2 mM, 20 mol %) was also observed to catalyze the reaction to the same extent as **3**·6NO_3, although no catalytic effect was found for (en)Pt(NO_3)$_2$ (1.2 mM, 20 mol %) (see Figure S9 in the Supporting Information).

At this point, is important to remark on the similarities and differences between the reactions catalyzed by metallacycle **3**·6NO_3 and ligand **4**·NO_3. First, the observation of comparable activities for **3**·6NO_3 and **4**·NO_3 suggests a similar catalytic mechanism involving the diazapyrenium moieties, with the cavity of **3**·6NO_3 not playing a key role in it. Nevertheless, in terms of practical use, metallacycle **3**·6NO_3 proved to be superior to ligand **4**·NO_3 as a catalyst. In this regard, laboratory-scale experiments using **1b**, NaN_3, and a catalytic amount of **3**·6NO_3 (10 mol %) in D_2O at rt showed that when the reaction was complete (after 10 h), it was possible to obtain the clean product **2** in 98% yield by a simple extraction with $CHCl_3$. The resulting aqueous phase containing **3**·6NO_3 and excess NaN_3 could be reutilized four more times in subsequent reactions upon the addition of **1b** (1 equiv) and NaN_3 (1 equiv) (Table 1). On the contrary, ligand **4**·NO_3 was not reusable because of its slight solubility in organic solvents.

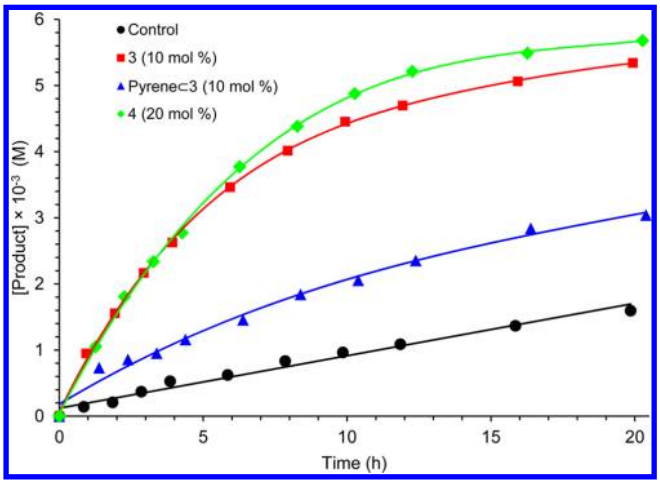


Figure 1. Kinetic data for the S_NAr reaction between **1b** (6 mM) and NaN_3 (60 mM) in D_2O/CD_3CN (4:1) at rt in the presence of **3**·6NO_3 (0.6 mM, 10 mol %) (red ■), **4**·NO_3 (1.2 mM, 20 mol %) (green ◆), or metallacycle **3**·6NO_3 (0.6 mM, 10 mol %) + pyrene (blue ▲) or in the absence of catalyst (black ●) as a control.

Table 1. Conversions and Yields for the Laboratory-Scale Reaction of 1b with NaN_3 in the Presence or Absence of 3·6NO_3[a]

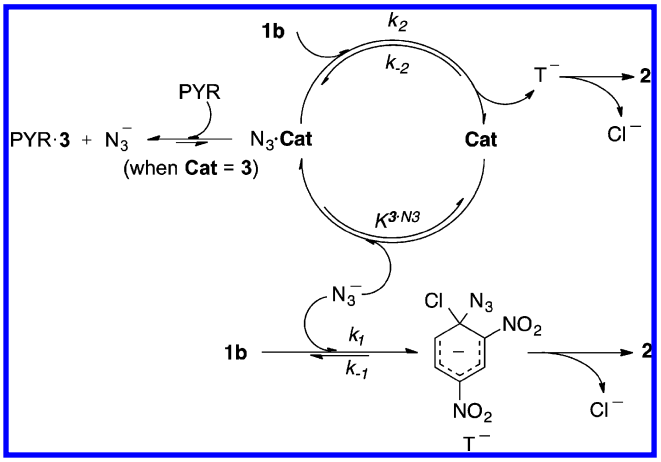
cycle	yield (%)[b]	time (days)
1	98	0.42
2	92	1.5
3	95	3
4	90	5
5	91	7
control[c]	4	0.42

[a]Reaction conditions: **1b** (70 mg, 10 mM), NaN_3 (100 mM), and **3**·6NO_3 (10 mol %) in D_2O at rt for the required time to reach a conversion of 100%. [b]Yields based on isolated product. [c]Reaction conditions: **1b** (70 mg, 10 mM) and NaN_3 (100 mM) in D_2O at rt.

In order to quantitatively evaluate the catalytic effect of metallacycle **3**·6NO_3 on the model S_NAr reaction, a kinetic model based on the reaction mechanism depicted in Scheme 2 was built. Applying the steady-state approximation to the

dx.doi.org/10.1021/jo402689p | J. Org. Chem. 2014, 79, 1265–1270

Scheme 2. Mechanistic Proposal for the Catalyzed S_NAr Reaction between 1b and NaN_3; The Inhibitory Effect Observed upon Addition of Pyrene (PYR) for Cat = 3·6NO_3 Is Also Represented



reaction intermediate and considering that the nucleophile concentration is in large excess over the aromatic substrate allows eq 1 for the observed rate constant k_{obs} to be derived:

$$k_{obs} = k_{obs}^{uncat} + k_{obs}^{cat} = k_{uncat}[N_3^-] + \frac{k_{cat}K^{3\cdot N_3}[\mathbf{3}][N_3^-]}{1 + K^{3\cdot N_3}[N_3^-]} \quad (1)$$

where k_{uncat} and k_{cat} are the rate constants for the uncatalyzed and catalyzed S_NAr reactions, respectively, and $K^{3\cdot N_3}$ represents the equilibrium constant for the formation of the azide–metallacycle complex. Therefore, the overall observed rate constant is given by the sum of two different contributions: the uncatalyzed process and the metallacycle-catalyzed reaction. Figure 2 shows the influence of azide concentration on the observed rate constant in the absence of added catalyst. As expected from eq 1, a linear dependence of k_{obs}^{uncat} on the nucleophile concentration was found, and the linear fit displayed in this figure gave the value $k_{uncat} = (9.04 \pm 0.02) \times 10^{-5}$ M^{-1} s^{-1}.

On the basis of eq 1, in the presence of added catalyst at a given azide concentration, k_{obs}^{cat} can be easily estimated from the difference between the observed rate constants in the presence and absence of metallacycle. Figure 2 also displays the fit of our experimental results to eq 1, with a satisfactory agreement between the kinetic data and the proposed rate law. Likewise, from this hyperbolic fit the values $k_{cat} = 0.085 \pm 0.023$ M^{-1} s^{-1} and $K^{3\cdot N_3} = 38.0 \pm 7.6$ M^{-1} were obtained.

At first glance, the kinetic experiments shown in Figure 2 for the catalyzed reaction exhibit a rather marked saturation profile. Thus, while the uncatalyzed reaction rate increases linearly with $[N_3^-]$ (Figure 2), the metallacycle-catalyzed reaction rate becomes gradually independent of the nucleophile concentration, that is, zeroth order in $[N_3^-]$. This leveling off can be easily justified in terms of the limited availability of azide associated to the catalyst. As an illustrative example, for a nucleophile concentration $[N_3^-] = 0.6$ M and the measured value of $K^{3\cdot N_3}$, it can be estimated that 96% of the added catalyst is associated to N_3^- to afford $3\cdot N_3^-$ complexes. Therefore, a further increase in the azide concentration will not lead to a substantial increase in $[3\cdot N_3^-]$ and accordingly will not increase the rate of the catalyzed reaction.

Most importantly, taking into account the values derived from Figure 2 yields a k_{cat}/k_{uncat} ratio of ~1000. Given the steady-state condition for the Meisenheimer intermediate ($\mathbf{T}^-$), it can be assumed that at no point is the equilibrium for the formation of $\mathbf{T}^-$ established, and hence, both steps (step 1: addition of the azide nucleophile; step 2: elimination of the halide leaving group) can be virtually treated as irreversible processes. In other words, $k_{cat} = k_2$ and $k_{uncat} = k_1$.[10] Consequently, it can be concluded that the presence of the metallacycle gives rise to a remarkable 1000-fold increase in the formation of the Meisenheimer complex. Additional spectroscopic experiments on the interaction between 3·6NO_3 and **1b** demonstrated the absence of preassociation between the metallacycle and the uncharged aromatic substrate, which rules out an unlikely situation where the reaction intermediate would be formed by the attack of the nucleophile on a **1b**·**3** complex.

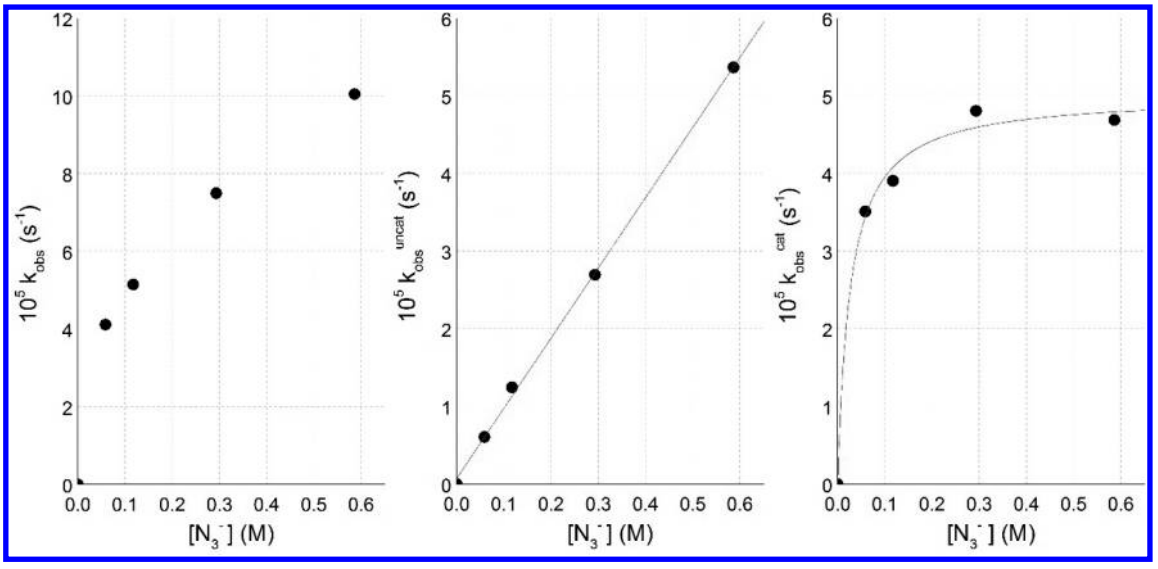


Figure 2. Influence of azide ion concentration on the overall (left), uncatalyzed (middle), and catalyzed (right) observed rate constants for the S_NAr reaction between **1b** and NaN_3 in D_2O/CD_3CN (4:1), where $k_{obs} = k_{obs}^{uncat} + k_{obs}^{cat}$. [**1b**] = 6 mM; [3·6$NO_3$] = 0.6 mM (10 mol %); T = 25 °C.

dx.doi.org/10.1021/jo402689p | J. Org. Chem. 2014, 79, 1265–1270

An alternative mechanistic proposal for the reaction between **1b** and NaN_3 would consist of a rate-limiting decomposition of the reaction intermediate (step 2 as rate-limiting). However, this alternative may be ruled out by comparing the results obtained for **1b** with those for halodinitrobenzenes **1a**, **1c**, and **1d**. As previously stated (vide supra), in the absence of catalyst, **1a** is fully transformed into the expected azide **2** (100% conversion in 22 h), while the corresponding substitution reactions for **1b**–**d** are much slower (33%, 44%, and 23% conversion, respectively, after 8 days). This sequence of halide leaving group abilities (F > Cl ≈ Br ≈ I) is often found in kinetic studies of S_NAr reactions involving nitroactivated aromatic halides. Where found,[11] this result establishes an addition–elimination mechanism for the S_NAr reaction in which the first step consists of rate-limiting nucleophilic attack to afford the σ adduct. Thus, groups with strong −I effects, such as fluorine, will likely promote the formation of the reaction intermediate, justifying the higher reactivity found for **1a**. Accordingly, for a hypothetical rate-limiting second step a much lower reactivity of **1a** compared with **1b**–**d** should be expected, which allows such a mechanism to be discarded.

In light of the kinetic results obtained for the catalytic system, the mechanistic proposal for the reaction between **1b** and NaN_3 (Scheme 2) involves the formation of the reaction intermediate $\mathbf{T}^-$ as the rate-limiting step. The desolvation experienced by the azide ion when it is associated to the positively charged diazapyrenium-based catalyst would make the nucleophile more reactive, thereby facilitating the formation of $\mathbf{T}^-$ and speeding up the overall process. The association of azide ion to **3** is an exergonic process, meaning that the binding of the nucleophile to the macrocycle lowers the free energy of the metallacycle–azide ion complex compared with that of the free nucleophile. Such a decrease logically must be accompanied by a greater lowering of the corresponding activation energy, without which the catalytic effect reported herein would not take place. In fact, experiments carried out with catalysts **3**·$6NO_3$ and **4**·NO_3 using an excess of $NaNO_3$ revealed a significant reduction in the catalytic effect that can be connected with disruption of the azide–catalyst association complex by the nitrate anions. This hypothesis is also substantiated by the observation of the catalytic efficiency of **3**·$6NO_3$ in different media [i.e., D_2O and D_2O/CD_3CN mixtures (4:1 and 1:1)]. The control reaction was clearly decelerated as the proportion of deuterium oxide increased (Table 2), which can be ascribed to the less effective solvation of the corresponding Meisenheimer intermediate $\mathbf{T}^-$ in water as well as the reduction of the nucleophilicity of the azide anion in protic solvents.[12] However, in the catalyzed reactions the reaction rate increases in the opposite direction with the concentration of D_2O because of the worse solvation of the azide–metallacycle complex by polar protic solvents.

Table 2. Conversions for the Reactions of 1b with NaN_3 at t = 10 h in the Presence or Absence of 3·$6NO_3$ in Different Solvents

	conversion (%)	
solvent	with 3·$6NO_3$[a]	control[b]
D_2O	100	5
D_2O/CD_3CN (4:1)	77	17
D_2O/CD_3CN (1:1)	59	51

[a]Conditions: **1b** (6 mM), NaN_3 (60 mM), and 3·$6NO_3$ (0.6 mM, 10 mol %) at rt. [b]Conditions: **1b** (6 mM) and NaN_3 (60 mM) at rt.

In order to gain further insights into the role of the cavity of 3·$6NO_3$ in the catalyzed reaction, substrate **1b** (clearly not a good guest for host 3·$6NO_3$), was replaced by 4-chloroquinoline (**5**), a substrate potentially able to react with NaN_3 by S_NAr as well as to get complexed by the metallacyclic host. Contrarily to the case of **1b**, changes in the NMR spectra of the system consistent with the formation of **5**⊂3·$6NO_3$ were observed upon addition of **5** to a solution of 3·$6NO_3$ in D_2O/CD_3CN (4:1). For instance, in the ^1H NMR spectra, resonances for the protons of the guest and protons located in the central part of the phenylene–diazapyrene system of 3·$6NO_3$ were shifted upfield as a consequence of their mutual shielding. On the other hand, resonances for the hydrogen nuclei of the pyridine rings of 3·$6NO_3$ were shifted to higher frequencies upon complexation, suggesting the occurrence of [C–H···π] interactions with **5**.

Kinetic studies showed significant differences between the reactions of **5** and NaN_3 catalyzed by the metallacycle 3·$6NO_3$ (0.6 mM, 10 mol %) and the ligand **4**·NO_3 (1.2 mM, 20 mol %) (Figure 3). Here, the assembly **5**⊂3·$6NO_3$ induced a decreased reaction rate in comparison with the S_NAr catalyzed by **4**·NO_3, giving evidence that the cavity of metallacycle 3·$6NO_3$ not only is not vital to the catalytic activity but also is potentially important as an allosteric-like regulatory center.[13]

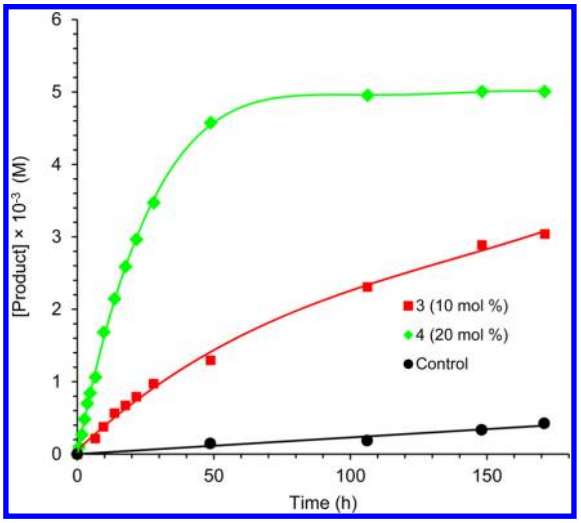


Figure 3. Kinetic data for the S_NAr reaction between **5** (6 mM) and NaN_3 (60 mM) in D_2O/CD_3CN (4:1) at rt in the presence of 3·$6NO_3$ (0.6 mM, 10 mol %) (red ■) or **4**·NO_3 (1.2 mM, 20 mol %) (green ◆) or in the absence of catalyst (black ●) as a control.

With the mechanistic proposal in our hands, and taking into account the evidence exonerating the cavity of the metallacycle 3·$6NO_3$ from responsibility for the observed catalytic activity, we decided to test the effect of a suitable nonreactive aromatic guest for receptor 3·$6NO_3$ on the behavior of the catalytic system. Pyrene (PYR)[8] was chosen for that purpose, and as a consequence of the host–guest complexation, it was found that the rate of the reaction catalyzed by 3·$6NO_3$ (10 mol %) decreased clearly (Figure 1), stressing the potential role of the cavity not on the observed catalysis but on the modulation of the catalytic activity.[14]

Considering the catalytic effect associated with the metallacycle 3·$6NO_3$ as a result of a specific cation-induced desolvation effect on the nucleophile, the supramolecular inhibition observed when a good guest is present in the system can be

dx.doi.org/10.1021/jo402689p | J. Org. Chem. 2014, 79, 1265–1270

explained by the formation of inclusion complexes. Thus, complexation would result in the modification of the electronic characteristics of the catalyst, rendering the diazapyrenium subunits less π-deficient because of the donation of electron density from the guest. This would reduce the amount of azide associated to the cation, reducing in consequence its desolvation and reactivity.[15] In other words, reversible host–guest complexation potentially allows the inhibitory activity to be modulated by the addition of guests with different binding strengths.

CONCLUSIONS

In summary, in the work presented here we have reported the performance of the Pt^{II} diazapyrenium-based metallacycle **3**·$6NO_3$ as a reusable substoichiometric catalyst for the S_NAr reaction between halodinitrobenzenes **1a–d** and NaN_3 at rt in aqueous media. The experimental results suggest that the catalytic effect is promoted by association of the azide to the diazapyrenium cationic subunits of the catalyst. Moreover, making use of the internal cavity and π-deficient aromatic subunits within the metallacycle, we have explored the inhibitory activity of pyrene in the catalytic system under study. The findings reported herein demonstrate that the formation of an inclusion complex has a regulatory effect over the system that results in allosteric-like inhibition of the S_NAr reaction. Ongoing studies are showing that the results reported in this work can be applicable to other nucleophiles and substrates in S_NAr reactions in water.

EXPERIMENTAL SECTION

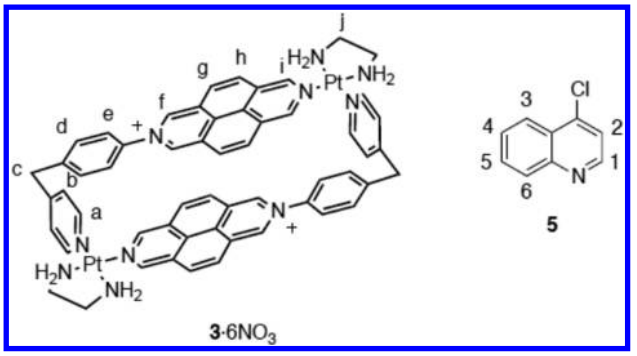
General Remarks. Compounds **1a–d**, sodium azide, and **5** were obtained from standard commercial vendors and used without any further purification. Metallacycle **3**·$6NO_3$ and ligand **4**·NO_3 were obtained according to published procedures.[8a] Likewise, 4-azidoquinoline (**6**) was prepared using the method reported in the literature.[16] Proton and carbon NMR spectra were recorded in Fourier mode at 300 or 500 MHz using the deuterated solvent as a lock and the residual protiated solvent as an internal standard.

Synthesis of 1-Azido-2,4-dinitrobenzene (2). A mixture of **1b** (70 mg, 0.32 mmol), NaN_3 (205 mg, 3.2 mmol), and **3**·$6NO_3$ (51 mg, 0.032 mmol) in D_2O (30 mL) was stirred at room temperature for 10 h. The reaction mixture was extracted with $CHCl_3$ (3 × 10 mL), and the combined organic layers were dried over magnesium sulfate and filtered. Finally, the solvent was removed under reduced pressure to give an amorphous pale-brownish solid (71 mg, 97%). The physical and spectral data of the obtained compound (FTIR, MS, ^1H and ^{13}C NMR) were found to be in good agreement with those previously reported for **2**.[17]

Characterization of the Inclusion Complex 5⊂3·$6NO_3$. An NMR tube containing **3**·$6NO_3$ (3.5 mM) and **5** (35 mM) in D_2O/CD_3CN (4:1) was prepared from stock solutions of **5** in CD_3CN and **3**·$6NO_3$ in D_2O. ^1H NMR (500 MHz, D_2O/CD_3CN 4:1 (v/v), 298 K): δ = 10.26 (s, H_i), 9.31 (s, H_f), 9.14 (d, J = 6.9 Hz, H_a), 8.76 (d, J = 4.8 Hz, H_1), 8.66 (d, J = 9.15 Hz, H_h), 8.30 (d, J = 9.15 Hz, H_g), 8.21 (d, J = 8.35 Hz, H_3), 8.04 (d, J = 8.45 Hz, H_6), 7.90 (t, J = 7.5 Hz, H_5), 7.82 (d, J = 6.9 Hz, H_b), 7.77 (t, J = 7.6 Hz, H_4), 7.70 (d, J = 4.8 Hz, H_2), 7.67 (d, J = 8.7 Hz, H_d), 7.47 (d, J = 8.7 Hz, H_e), 4.37 (s, H_c), 3.11 (s, H_j) ppm.

Kinetic Measurements for the Reaction between 1b and NaN_3. *Control Reaction.* In order to perform the kinetic measurements for the uncatalyzed reaction, 1 mL samples suitable for ^1H NMR analysis containing **1b** (6 mM) in D_2O/CD_3CN (4:1) were prepared from a stock solution of **1b** in CD_3CN. The sodium azide was added in solid form to initiate the reaction.

Catalyzed Reaction. For catalyzed reactions, 1 mL samples suitable for ^1H NMR analysis containing **1b** (6 mM) and the corresponding



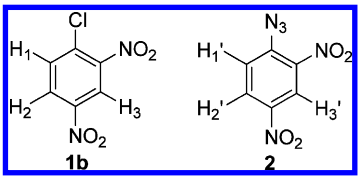
catalyst **3**·$6NO_3$ (0.6 mM) or **4**·NO_3 (1.2 mM) in D_2O/CD_3CN (4:1) were prepared from stock solutions of **1b** in CD_3CN and **3**·$6NO_3$/**4**·NO_3 in D_2O. The sodium azide was added in solid form to initiate the reaction.

Control Reaction in the Presence of (en)Pt(NO_3)$_2$. Samples (1 mL) suitable for ^1H NMR analysis containing **1b** (6 mM) and (en)Pt(NO_3)$_2$ (1.2 mM) in D_2O/CD_3CN (4:1) were prepared from stock solutions of **1b** in CD_3CN and (en)Pt(NO_3)$_2$ in D_2O. The sodium azide was added in solid form to initiate the reaction.

Control Reaction in the Presence of $NaNO_3$. Samples (1 mL) suitable for ^1H NMR analysis containing **1b** (6 mM) and $NaNO_3$ (1.2 mM) in D_2O/CD_3CN (4:1) were prepared from stock solutions of **1b** in CD_3CN and $NaNO_3$ (0.6 mM) in D_2O. The sodium azide was added in solid form to initiate the reaction.

Catalyzed Reaction in the Presence of Pyrene. Samples (1 mL) suitable for ^1H NMR analysis containing **1b** (6 mM), and pyrene⊂**3**·$6NO_3$ (0.6 mM) in D_2O/CD_3CN (4:1) were prepared from stock solutions of **1b** in CD_3CN and pyrene⊂**3**·$6NO_3$ (0.6 mM) in D_2O/CD_3CN (4:1). The sodium azide was added in solid form to initiate the reaction.

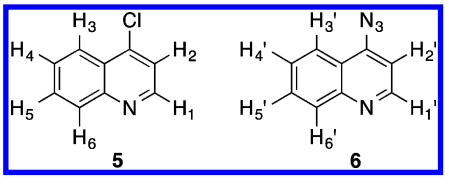
In all cases, the progress of the reaction was monitored by ^1H NMR spectroscopy at 298 K. The concentrations of **1b** and azide **2** were determined by relative integrations of the peaks at δ = 8.17 ppm (d, J = 9.0 Hz, H_1; substrate **1b**) and δ = 7.94 ppm (d, J = 9.0 Hz, H_1'; reaction product **2**) as functions of time.



Kinetic Measurements for the Reaction between 5 and NaN_3. *Control Reaction.* For kinetic measurements, 1 mL samples suitable for ^1H NMR analysis containing **5** (6 mM) in D_2O/CD_3CN (4:1) were prepared from a stock solution of **5** in CD_3CN. The sodium azide was added in solid form to initiate the reaction.

Catalyzed Reactions. For kinetic measurements, 1 mL samples suitable for ^1H NMR analysis containing **5** (6 mM) and **3**·$6NO_3$ (0.6 mM) or **4**·NO_3 (1.2 mM) in D_2O/CD_3CN (4:1) were prepared from stock solutions of **5** in CD_3CN and **3**·$6NO_3$/**4**·NO_3 in D_2O. The sodium azide was added in solid form to initiate the reaction.

In all cases, the progress of the reaction was monitored by ^1H NMR spectroscopy at 298 K. The concentrations of **5** and **6** were determined by relative integrations of the peaks at δ = 7.91 ppm (d, J = 5.0 Hz, H_2; substrate **5**) and δ = 7.58 ppm (d, J = 5.0 Hz, H_2'; reaction product **6**) as functions of time.



dx.doi.org/10.1021/jo402689p | J. Org. Chem. 2014, 79, 1265–1270

■ ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C, and 2D NMR spectra for the inclusion complex **5**⊂**3**·6NO_3, references, and results of representative kinetic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: carlos.peinador@udc.es.

*E-mail: jose.maria.quintela@udc.es. Fax: +34 981 167 065. Tel: +34 981 167 000.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by Ministerio de Ciencia e Innovación and FEDER (CTQ2010-16484/BQU). E.M.L.-V. thanks Ministerio de Ciencia e Innovación (FPI Program).

■ REFERENCES

(1) (a) Marchetti, L.; Levine, M. *ACS Catal.* **2011**, *1*, 1090. (b) Vriezema, D. M.; Aragonès, M. C.; Elemans, J. A. A. W.; Cornelissen, J. J. L. M.; Rowan, A. E.; Nolte, R. J. M. *Chem. Rev.* **2005**, *105*, 1445.

(2) (a) Debata, N. B.; Tripathy, D.; Chand, D. K. *Coord. Chem. Rev.* **2012**, *256*, 1831. (b) Beves, J. E.; Blight, B. A.; Campbell, C. J.; Leigh, D. A.; McBurne, R. T. *Angew. Chem., Int. Ed.* **2011**, *50*, 9260. (c) Chakrabarty, R.; Mukherjee, P. S.; Stang, P. J. *Chem. Rev.* **2011**, *111*, 6810. (d) Safont-Sempere, M. M.; Fernández, G.; Würthner, F. *Chem. Rev.* **2011**, *111*, 5784. (e) Kumar, A.; Sun, S.-S.; Lees, A. J. *Coord. Chem. Rev.* **2008**, *252*, 922.

(3) (a) Lin, W. In *Supramolecular Catalysis*; van Leeuwen, P. W. N. M., Ed.; Wiley-VCH: Weinheim, Germany, 2008; p 93. (b) Yoshizawa, M.; Klosterman, J. K.; Fujita, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3418. (c) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *Acc. Chem. Res.* **2009**, *42*, 1650. (d) Koblenz, T. S.; Wassenaar, J.; Reek, J. N. H. *Chem. Soc. Rev.* **2008**, *37*, 247.

(4) (a) Kang, J.; Rebek, J., Jr. *Nature* **1997**, *385*, 50. (b) Iwasawa, T.; Hooley, R. J.; Rebek, J., Jr. *Science* **2007**, *317*, 493. (c) Butterfield, S. M.; Rebek, J., Jr. *Chem. Commun.* **2007**, 1605.

(5) (a) Merlau, M. L.; Mejia, M. d. P.; Nguyen, S. T.; Hupp, J. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 4239. (b) Yoon, H. J.; Mirkin, C. A. *J. Am. Chem. Soc.* **2008**, *130*, 11590. (c) Yoon, H. J.; Kuwabara, J.; Kim, J.-H.; Mirkin, C. A. *Science* **2010**, *330*, 66. (d) Noh, T. H.; Heo, E.; Park, K. H.; Jung, O. S. *J. Am. Chem. Soc.* **2011**, *133*, 1236. (e) Hastings, C. J.; Backlund, M. P.; Bergman, R. G.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2011**, *50*, 10570. (f) Amouri, H.; Desmarets, C.; Moussa, J. *Chem. Rev.* **2012**, *112*, 2015. (g) He, Q.-T.; Li, X.-P.; Chen, L.-F.; Zhang, L.; Wang, W.; Su, C.-Y. *ACS Catal.* **2013**, *3*, 1.

(6) (a) López-Vidal, E. M.; Blanco, V.; García, M. D.; Peinador, C.; Quintela, J. M. *Org. Lett.* **2012**, *14*, 580. (b) Blanco, V.; García, M. D.; Platas-Iglesias, C.; Peinador, C.; Quintela, J. M. *Chem. Commun.* **2010**, *46*, 6672. (c) Peinador, C.; Blanco, V.; Quintela, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 920. (d) Blanco, V.; Gutierrez, A.; Platas-Iglesias, C.; Peinador, C.; Quintela, J. M. *J. Org. Chem.* **2009**, *74*, 6577. (e) Peinador, C.; Pía, E.; Blanco, V.; García, M. D.; Quintela, J. M. *Org. Lett.* **2010**, *12*, 1380. (f) Peinador, C.; Blanco, V.; García, M. D.; Quintela, J. M. In *Molecular Self-Assembly: Advances and Applications*; Li, A. D. Q., Ed.; Pan Stanford Publishing: Singapore, 2012; p 351.

(7) D'Anna, F.; Marullo, S.; Noto, R. *J. Org. Chem.* **2008**, *73*, 6224.

(8) (a) Blanco, V.; García, M. D.; Terenzi, A.; Pía, E.; Fernández-Mato, A.; Peinador, C.; Quintela, J. M. *Chem.—Eur. J.* **2010**, *16*, 12373. (b) Alvariño, C.; Pía, E.; García, M. D.; Blanco, V.; Fernández, A.; Peinador, C.; Quintela, J. M. *Chem.—Eur. J.* **2013**, *19*, 15329.

(9) The D_2O/CD_3CN (4:1) mixture was employed in order to ensure the solubilization of all the reactants, as it was necessary to do the kinetic study in a homogeneous medium.

(10) The rate-limiting step of an S^NAr is determined by the relative rates of the expulsion of the nucleophile and the leaving group from the Meisenheimer intermediate. If one group leaves faster than the other, the step involving the poorer leaving group (in this case, the azide ion) is rate-determining. This means that the reverse direction of the equilibrium for the formation of the reaction intermediate must be slower than that of its irreversible collapse, which confirms that k_{uncat} and k_{cat} can be identified as the rate constants in the forward direction in the equilibria for the formation of $\mathbf{T}^-$ (k_1 and k_2, respectively).

(11) This sequence of reactivity is also known as the "element effect". See: Bunnett, J. F.; Garbisch, E. W., Jr.; Pruitt, K. M. *J. Am. Chem. Soc.* **1957**, *79*, 385.

(12) (a) Miller, J.; Parker, A. J. *J. Am. Chem. Soc.* **1961**, *83*, 117. (b) Alexander, R.; Ko, E. C. F.; Parker, A. J.; Broston, T. J. *J. Am. Chem. Soc.* **1968**, *90*, 5049.

(13) For instance, Shinkai et al. reported this kind of "remote control" over the reactivity of a flavin analogue by means of metal complexation to a distal crown ether attached to the coenzyme core. See: Shinkai, S.; Kameoka, K.; Ueda, K.; Manabe, O. *J. Am. Chem. Soc.* **1987**, *109*, 923.

(14) This inhibitory effect could not be studied with ligand **4**·NO_3 because no complexation between **4**·NO_3 and pyrene occurs, and consequently, no solubilization of pyrene was detected.

(15) Pliego, J. R., Jr.; Pilo-Veloso, D. *Phys. Chem. Chem. Phys.* **2008**, *10*, 1118.

(16) Budyka, M. F.; Biktimrova, N. V.; Gavrishova, T. N.; Laukhina, O. D.; Zemtsov, D. B. *J. Photochem. Photobiol., A* **2005**, *173*, 70.

(17) Bailey, A. S.; Case, J. R. *Tetrahedron* **1958**, *3*, 113.